Finnish Advisory Board on Research Integrity
Matej Oresic et al
The Journal of Experimental Medicine

Reference: Decision of launching preliminary inquiries 26th of February 2016 and 3rd of March 2016

DECISION, THE PROCESS FOR HANDLING ALLEGED VIOLATIONS OF THE RESPONSIBLE CONDUCT OF RESEARCH

Article: Dysregulation of lipid and amino acid metabolism precedes islet autoimmunity in children who later progress to type 1 diabetes, J Exp Med. 2008 Dec 22;205(13):2975-84. doi: 10.1084/jem.20081800. Epub 2008 Dec 15.

Authors: Oresic M1, Simell S, Sysi-Aho M, Näntö-Salonen K, Seppänen-Laakso T, Parikka V, Katajamaa M, Hekkala A, Mattila I, Keskinen P, Yetukuri L, Reinikainen A, Lähde J, Suortti T, Hakalax J, Simell T, Hyöty H, Veijola R, Ilonen J, Lahesmaa R, Knip M, Simell O.

Helsingin Sanomat published news 7th of February 2016 that questioned whether VTT had made an unqualified investigation of the above mentioned article in 2014. Due to this suspicion VTT decided to launch a preliminary inquiry to find out if there could be any proof of violations in this article of the responsible conduct of research according to the Finnish Advisory on research Integrity.

VTT has committed itself to follow the RCR guidelines in the handling of alleged violations of the responsible conduct of research. Since the guidelines have been renewed after releasing the above mentioned article the allegations were investigated against the RCR 2002 guidelines (violations of good scientific practice). However the processes of preliminary inquiries were conducted according to the RCR 2012 rules.

Professor Ville-Petteri Mäkinen (South Australian Health and Medical Research Institute, SAHMRI) and Professor Ilpo T Huhtaniemi (Imperial College of London Faculty of Medicine, Department of Surgery & Cancer, Emeritus Professor of Reproductive Endocrinology) have been appointed to to accomplish in the assessment of possible violations of good scientific practice 26th of February 2016.
Professor Jon Florholmen (MD PhD Professor, Head, Research Group of Gastroenterology and Nutrition, Institute Clinical Medicine, Norwegian Arctic University,Tromsø, Norway) was appointed 3rd of March 2016.

Professors Ville-Petteri Mäkinen, Ilpo T Huhtaniemi and Jon Florholmen have accomplished the assessments according to the Finnish Advisory on Research Integrity (RCR rules). Written reports of these assesments are attached to this decision.

Professor Ville-Petteri Mäkinen concludes in his assessment (1.4.2016):

> *3 Conclusions*
> *3.1 Did the authors fabricate data?*
> *I found no suspicious features in the article that would suggest any of the samples, measurements or molecular concentrations were fabricated. All the sample procedures and technical details are consistent with accepted practices in the field, there are no*

outrageous claims of superior accuracy and the lipid species included in the study were, if anything, conservatively filtered to include the best quality portion of the data. My overall impression from the hundreds of concentrations curves provided by VTT fits with the nature of typical metabolomics data that come from clinical samples. The age and seasonal distribution of the participating children are unremarkable, although based on the limited information provided it is impossible to say if they represented typical children in the population-based parent cohort.

3.2 Did the authors tamper with statistical analyses?
I found no convincing evidence that any of the statistical analyses were falsified so as to promote an erroneous conclusion. There were several technical issues that need attention, but it is important to remember that the first author (as far as I know) is a metabolomics expert, not a statistician, and the majority of the other authors are clinicians or basic biologists. Although I have not followed the case in the media in detail, nor do I have first-hand knowledge of what happened at VTT, the background information I do have points to communication problems and the subsequent disintegration of the research group. To this backdrop, it is perhaps not surprising that the quality of the work may have sufferedin thetoxic environment, which would easily explain the technical problems in the article. The partial re-analyses by the two independent statisticians corroborated the strongest findings, which is further indication against deliberate tampering.

3.3 Did the authors deceive readers by misrepresenting data?
I found evidence of poorly represented results in the main text, and exaggerated claims in the title and abstract, but I cannot unequivocally state that they constitute a fraud. There is a reasonable possibility that some of the problemswere due to lack of experience and some were due to the break-down in cross-disciplinary communication. It is important to remember that human metabolomics studies were very much an emerging field in 2008, and there was no collective effort to improve thereliability of articles. Indeed, I still get manuscripts for peer-review with grandiose claims in the title only to find that the statistical analyses are poorly conducted and the interpretations have no logical basis. In most cases the peer-review systemworks and authors improve the quality of their work, as happened here with the first five rejections by the top-tier journals. While some readers might get the wrong impression from a superficial reading of the article by Oresic and co-authors, I am of the opinion that despite the bombastic first page and technical issues, there is enough information within the textand figuresto get a balanced view of the findings.

Professor Ilpo Huhtaniemi summarises his assessment as follows (13.4.2016):

I did not find in the publication signs of data manipulation, neither gross miss- and overinterpretation of results or unrealistic conclusions. The former could ultimately only be detected by scrutiny of the original laboratory log books and raw data. Manipulated data are typically 'too good to be true'. This is not the case with the current paper, the results are merely 'too modest to be false', and qualitatively quite expected. The study is by no means perfect. It is based on a very small material to be analysed for parameters with notoriously large interindividual variability, resulting, as expected, in marginally meaningful findings. The statistical analysis of the data was rather primitive with low power. More sophisticated statics could have revealed much more from this complex data set. I identified several erroneous interpretations in Results and Discussion, stating non-significant changes as changes (at $p<0.06$ and $p<0.09$). There is therefore some evidence of superficial data interpretation, because all conclusions did not strictly adhere to the results. I found the highly criticised Fig. 2 in the context of this publication acceptable, but its limitations were insufficiently explained. The discussion is in places rather speculative (e.g. Fig. 6), but mainly realistic, taking into account the preliminary nature and small size of the study. In my opinion the paper does not contain unrealistic conclusions. The main

message of the study, i.e. that some metabolomics changes appear to occur in children before seroconversion, is not jeopardised by the flaws in details that I pointed out.

To conclude, I was not able to detect unequivocal proof of fraud (data tampering, falsification, or erroneous reporting) in this publication. Neither did it contain such excessive interpretation of results or unrealistic conclusions that would deviate from the normal writing style of scientific publications.

Professor Jon Florholmen (5.5.2016) summarises:

New and original data are presented – and potential biomarkers of early events of the autoimmune events in type 1 diabetes have been proposed. Whether these potential biomarkers will be documented in future reports from other research groups are an open question also as stated in the Conclusion. There is some minor weakness in the paper, but I would as a potential reviewer- proposed some minor corrections before acceptance.

I have no indications of any misconduct. By the worse, the biomarkers documented may not fit with other future reports, but this was especially taken into consideration by the authors.

This evaluation has been performed after discussion and evaluations also by specialists in mass spectrometry and bioinformatics- all evaluations have been confidential performed.

According to 2002 RCR guideline violations of good scientific practice have been classified into two categories, which are misconduct in science and fraud in science. Fraud in science means deceiving the research community and often also decision-makers. It is to give false information or present false results to the research community or to disseminate them for instance in a publication, in a paper presented at a scientific conference, in a manuscript submitted for publication or in a grant application.

Misconduct in science is manifested as gross negligence and irresponsibility especially in the conduct of research. Other examples of misconduct in science include understatement of other researchers' contribution to a publication and negligence in referring to earlier findings; careless, and hence misleading, reporting of research findings and the methods used; negligence in recording and preserving results; publication of the same results several times as new; and misleading the research community about one's own research.

The conclusions from all these three independent evaluations were that they were not able to detect violations of good scientific practice in this publication. Mäkinen found "no suspicious features in the article that would suggest any of the samples, measurements or molecular concentrations were fabricated" nor did he found evidence "that any of the statistical analyses were falsified so as to promote an erroneous conclusion". While Mäkinen found "evidence of poorly represented results in the main text, exaggerated claims in the title and abstract" he cannot state that they constitute fraud. Huhtaniemi states that "neither did it contain such excessive interpretation of results nor unrealistic conclusions that would deviate from the normal writing style of scientific publications".Professor Florholmen notices that "there are some minor weakness in the paper" but he found no indications of any misconduct.

All three evaluation reports and the draft of this decision to discontinue the investigation process was sent to all authors and they were given an opportunity to comment the decision by giving VTT a written statement by 14th of June 2016. VTT has received 3 statements (attached). One of them is stating satisfaction with the decision and two suggesting that sharing the anonymized processed data as a

supplementary material to the article would be best and most transparent solution allowing anyone to base their claims on the actual data.

The RCR 2012 guidelines state that on the basis of the preliminary inquiry if the allegation turns out to be unfounded a reasoned decision to discontinue the investigation process should be made. Therefore, on the basis what the aforesaid three evaluations conclude – there are no indications of violations of good scientific practise - Antti Vasara, President & CEO of VTT decides to discontinue the investigation of this article.

However, as suggested in two of the written statements received, VTT agrees to give permission to depositing and sharing the anonymized processed data as a supplementary material to the article - as far as the legislation of personal data allows it - and if other owners of the data (clinicians) will agree on that.

Any party dissatisfied with this decision can request a statement from the Finnish Advisory Board on Research Integrity within six months of being notified of the decision (according to point 12 in the RCR process).

Antti Vasara
President & CEO

Attachements:

- Evaluation of Professor Ville Petteri Mäkinen, 1.4.2016
- Evaluation of Professor Ilpo Huhtaniemi 13.4.2016
- Evaluation of Professor Jon Florholmen 5.5.2016
- Written statements: Sysi-Aho 10.6.2016, Orešič 10.6.2016, Orešič 14.6.2015